DOCKET NO.: UPN-3904 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Alexander V. Kachur, Sydney M. Evans, Chyung-Yann Shiue, Ian R. Baird, Kirsten A. Skov, William R. Dolbier, An-Rong Li, Brian R. James
Application No.: 09/648,306
Filing Date: August 25, 2000
For: DETECTION OF HYPOXIA

Confirmation No.: 6906
Group Art Unit: 1626
Examiner: Sonya N. Wright

EXPRESS MAIL LABEL NO: EV 325642715 US
DATE OF DEPOSIT: July 3, 2003

EV325642715US

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF

1. Transmitted herewith in triplicate is the APPEAL BRIEF in this application with respect to the Notice of Appeal filed on **March 5, 2003**.

2. STATUS OF APPLICANT

☒ Applicant(s) has previously claimed small entity status under 37 CFR § 1.27.

☐ Applicant(s) by its/their undersigned attorney, claims small entity status under 37 CFR § 1.27 as:

☐ an Independent Inventor

☐ a Small Business Concern

☐ a Nonprofit Organization.

3. EXTENSION OF TERM

The proceedings herein are for a patent application and the provisions of 37 CFR § 1.136 apply.

☒ Applicant petitions for an extension of time under 37 CFR § 1.136 (fees: 37 CFR § 1.17(a)-(d)) for the total number of months checked below:

	SMALL ENTITY		NOT SMALL ENTITY	
	RATE	FEE	RATE	FEE
☐ ONE MONTH EXTENSION OF TIME	$55	$0.00	$110	$0.00
☒ TWO MONTH EXTENSION OF TIME	$205	$205.00	$410	$0.00
☐ THREE MONTH EXTENSION OF TIME	$465	$0.00	$930	$0.00
☐ FOUR MONTH EXTENSION OF TIME	$725	$0.00	$1450	$0.00
☐ FIVE MONTH EXTENSION OF TIME	$985	$0.00	$1970	$0.00
☐ LESS ANY EXTENSION FEE ALREADY PAID	minus	($0.00)	minus	($0.00)
☒ APPEAL BRIEF	$160	$160.00	$320	$0.00
TOTAL FEE DUE		$365.00		$0.00

4. FEE PAYMENT

☒ A check in the amount of **$365.00** is attached. Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

☐ Please charge Deposit Account No. 23-3050 in the amount of **$ .00**. This sheet is attached in duplicate.

5. FEE DEFICIENCY

☒ If any additional extension and/or fee is required, this is a request therefor and to charge Deposit Account No. 23-3050.

☒ If any additional fee for claims is required, charge Deposit Account No. 23-3050.

6. ☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to deposit account 23-3050. This sheet is provided in duplicate.

Date: July 3, 2003

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DOCKET NO.: UPN-3904 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Cameron J. Koch, Alexander V. Kachur, Sydney M. Evans, Chyng-Yann Shiue, Ian R. Baird, Kirsten A. Skov, William R. Dolbier, An-Rong Li, Brian R. James

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Washington, DC 20231

APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. § 1.192

Applicants appeal the September 5, 2002 Final Rejection of claims 20-22 and 27-32 of the above-identified patent application. A timely Notice of Appeal with the appropriate fee was filed on March 5, 2003.

I. REAL PARTY IN INTEREST

Based on information supplied by Applicants and to the best of the undersigned's knowledge, the real party in interest in the above-identified patent application is the Trustees of the University of Pennsylvania, a non-profit corporation of Pennsylvania, U.S.A., which is

the assignee of Cameron J. Koch, Alexander V. Kachur, Sydney M. Evans, Chyng-Yann Shiue, Ian R. Baird, Kirsten A. Skov, William R. Dolbier, An-Rong Li, and Brian R. James.[1]

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to Applicants, Applicants' legal representative, or the assignee that will directly affect, be directly affected by, or have a bearing on the Board's decision in the pending Appeal.

III. STATUS OF CLAIMS

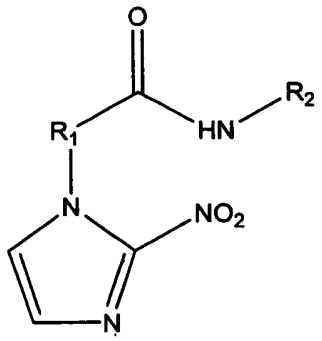
Claims 20-22 and 27-32 are pending in this patent application and are the subject of this appeal. These claims appear in Appendix A. Claims 1-14, 23-26 have been cancelled.

IV. STATUS OF AMENDMENTS

There have been no amendments filed after the Final Rejection.

V. SUMMARY OF INVENTION

The present invention is directed to methods of detecting tissue hypoxia using compounds having the formula:



[1] Applicants commented on the status of the inventor assignments of the present application in footnote 1 of the December 14, 2001 office action response. The current assignment status is reflected as it stands with the PTO in this section.

wherein R_1 is CH_2; and R_2 has the formula $CH_2CX_2CHX_2$, wherein X is halogen or hydrogen and at least 1 carbon atom of said alkyl group is bound with at least one ^{18}F. The methods involve administering to a mammal a compound of the invention dissolved or dispersed in a suitable pharmaceutical carrier or diluent. After partially clearing the mammal, the compound is taken up preferentially through the bioreductive metabolism of hypoxic cells. The portion of the mammal containing the tissue is analyzed non-invasively through positron emission tomography (PET). For use in PET, the compounds used in these methods must be formulated with the positron emitting isotope ^{18}F. (Specification, p. 10, lines 1-12).

VI. ISSUES

There is one issue that remains for resolution in this appeal:

Whether the Examiner erred in rejecting claims 20-22 and 27-32 as being obvious under 35 U.S.C. § 103(a) in view of the generalized disclosure of U.S. Patent No. 5,540,908 to Koch *et al.* (hereinafter "the Koch patent").

VII. GROUPING OF CLAIMS

With respect to the rejection under 35 U.S.C. § 103(a), claims 20-21 stand or fall together and claims 22 and 27-32 stand or fall together.

VIII. ARGUMENT

There is no evidence of record indicating that one of ordinary skill in the art would have been motivated to modify the generalized teachings of the Koch patent in a way that would have produced the claimed invention. Accordingly, the rejection of claims 20-22 and 27-32 for alleged obviousness is improper and should be withdrawn.

To establish a *prima facie* case of obviousness, three requirements must be satisfied: (1) there must be some suggestion or motivation to modify the reference or to combine the reference's teachings; (2) there must be a reasonable expectation of success for achieving the claimed invention and its particular results; and (3) the prior art reference(s) must teach or suggest all the claim limitations. *See In re Vaeck*, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991). Moreover, a prior art reference must be considered in its entirety, including disclosures that would teach away from the claimed invention. *See W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

The Examiner failed to consider the teachings of the Koch patent in its entirety and to satisfy each of the requirements needed to establish a *prima facie* case of obviousness.

A. The Examiner Has Failed To Show That The Koch Patent, In Its Entirety, Teaches or Suggests The Claimed R_2 Substituent.

The Examiner mistakenly alleges that there is motivation to use the Koch patent's general teachings relating to using a class of compounds to detect tissue hypoxia to obtain the present invention. As a basis for this allegation, the Examiner cites the Koch patent's generic teachings of an amide nitrogen substituent "containing 1 to 6 carbons, and preferably having up to 6 halogen atoms." (the Koch patent, at column 6, lines 21-23). This is an insufficient basis for rejecting the present claims that define compounds wherein the R_2 substituent, has the formula $CH_2CX_2CHX_2$, wherein X is halogen or hydrogen and at least 1 carbon atom of said alkyl group is bound with at least one ^{18}F atom. Although the claimed R_2 substituent may be encompassed by the Koch patent's generic formula, more is needed to render the claimed invention obvious. *In re Baird*, 16 F.3d 380, 382, 29 U.S.P.Q. 2d 1550, 1552 (Fed. Cir. 1994) ("the fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious").

In *Baird*, the Board affirmed an examiner's rejection of a claim as being obvious on the grounds that a reference disclosed a generic diphenol formula that encompassed three dicarboxylic acids specifically recited in the claim. *See id.* The Federal Circuit reversed the Board's decision because of the large number of compounds disclosed by the reference at issue. *See id.* The Federal Circuit also reasoned that the cited reference taught away from the Applicant's claim because it focused on other, more complex compounds. *See id.* at 383-384. Similarly here, the Koch patent's generic teachings of an "alkyl group containing 1 to 6 carbons, and preferably having up to 6 halogen atoms," (*see* Koch patent, at column 6, lines 21-23), suggests a multiplicity of alkyl substituents. What the Examiner was required to provide, and failed to provide, is "some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *See In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q. 2d 1635, 1637 (Fed. Cir. 1998).

The Examiner's use of the above-identified generic teaching of the Koch patent is insufficient to discharge the Examiner's burden. Because the R_2 groups of the claimed compounds differ from the Koch patent compounds, the Examiner needed to provide a more specific showing. For example, the R_2 groups of the claimed compounds exhibit difficult chemical properties due, in part, to the nature of their multiply halogenated alkyl chains. The examiner did not address these differences in properties and synthetic methods attendant to these different side chains. Further, the different characteristics of the ^{18}F and ^{19}F atoms present in the claimed compounds were not addressed by the Examiner. For example, the natural fluorine isotope, ^{19}F, and the radioactive isotope, ^{18}F, differ in many aspects, and especially in the methods of synthesis and the methods of incorporating those isotopes into compounds. ^{18}F is a highly radioactive isotope that can only be prepared using a cyclotron. This isotope has a short half-life and, consequently, has to be incorporated into the molecule

of interest and used within hours. This poses a challenge when using this isotope in compounds. This challenge is particularly acute with the claimed compounds because of their multiply halogenated alkyl chains. There has been no showing by the Examiner of any motivation in the Koch patent or otherwise that takes these challenges into account. Without such a showing, the Examiner's generalizations fail to establish a *prima facie* case of obviousness.

Applicants discuss these various difficulties and methods of synthesis of the various claimed R_2 groups in the present application, for example, on page 14, line 11-page 15, line 1. Example 15 discusses the various problems encountered in synthesizing the compounds of the claimed invention, none of which appear in the Koch patent. Examples 10-14 further disclose methods of preparing and using compounds of the present invention having ^{18}F atoms for PET. Notably, there is no disclosure in the Koch patent of any of these problems nor is there any disclosure of synthetic methods that may be used to address and overcome these problems. Accordingly, the Koch patent cannot render the claimed invention obvious.

The Examiner has failed to establish that the Koch patent provides motivation to obtain the claimed invention given its disclosure and absent the teachings of the present application. "A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Kotzab*, 217 F.3d 1365, 1369, 55 U.S.P.Q. 2d 1313, 1316 (Fed. Cir. 2000). "The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time." *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q. 2d 1614, 1617 (Fed. Cir. 1999) (quoting *Interconnect Planning Corp. v. Feil*, 774 F. 2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985). "In other words, the examiner must show reasons

that the skilled artisan, confronted with the same problem as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *In re Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q. 2d 1453, 1458 (Fed. Cir. 1998). The Examiner failed to do so.

B. The Koch Patent Does Not Teach, Suggest, or Motivate One To Arrive At The Claimed Alkyl Group.

A review of what the Koch patent teaches shows that the patent's focus is on compounds that differ from the kind embodied in the present claims. In the context of its general teachings, the Koch patent guides one skilled in the art to its preferred alkyl group--$CH_2CF_2CF_3$. (*See* the Koch patent, at column 6, lines 23-26). The specification then describes the compounds of the "greatly preferred" embodiments as 2(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide (referred to as EF5). (*See* the Koch patent, at column 5, lines 11-19). In all subsequent preferred embodiments, the Koch patent explicitly teaches that the amide nitrogen substituent contains the five fluorine atoms of the EF5 formula and three fluorine atoms on the terminal carbon atom. (*See* the Koch patent, at column 6, lines 23-26, 39-42; column 7, lines 5-7; column 12, lines 21-24; column 14, lines 20-23) .

The examples in the Koch patent reinforce the differences between the claimed invention and the Koch patent's amide nitrogen substituent. For instance, all 12 examples contained in the Koch patent focus on compounds where the alkyl group contains five fluorine atoms – three fluorine atoms on the terminal carbon and two fluorine atoms on the secondary – the preferred EF5 compounds. By contrast, the claimed R_2 substituent does not have five fluorine atoms, but rather, at most, a total of four fluorine atoms with at least one of those fluorine atoms being the ^{18}F isotope. The only disclosure in the Koch patent of a compound with an amide nitrogen substituent having three fluorine atoms is in the

specification at column 23, lines 39-42. Notably, this disclosure is one where all three fluorine atoms are on the terminal carbon atom, unlike the claimed invention, which only allows for two fluorine atoms on the terminal carbon atom. Neither the Koch patent's disclosure nor the examples teach or suggest the compounds of the present invention having only two fluorine atoms on the terminal carbon. Similarly, neither the Koch patent's disclosure nor the examples give any hint of how to synthesize the compounds of the present invention where the terminal carbon contains, at most, two fluorine atoms that may vary in kind. Indeed, the Examiner has pointed to no such teaching or suggestion in the Koch patent or any specific teaching or suggestion that would lead one skilled in the art to make the claimed compounds where the terminal carbon contains only two fluorine atoms.

Further, the teachings of the Koch patent are clear – the amide nitrogen substituent must preferably contain five fluorine atoms, with three fluorine atoms on the R_2 terminal carbon. In addition to the discussion of the preferred embodiments, the claims make it clear that this is the focus of the Koch patent. Independent claims 14, 20, and 26, for example, require an "alkyl group having up to about 6 halogen atoms, wherein said alkyl group has the formula $CHXCX_2CY_3$ where X is halogen or hydrogen and Y is fluorine." Consistent with the teachings of the specification, this formula requires three fluorine atoms on the terminal carbon. Further, the Koch patent's remaining independent claims require that the terminal carbon have attached either fluorine or bromine. (*See* Koch patent, claims 1, 7, and 29). There are no claims that allow for only two fluorine atoms attached along with a hydrogen atom to the terminal carbon as recited in the present claims.

C. The Examiner Has Failed To Present Adequate Motivation For A Showing of Obviousness.

The Examiner failed to provide adequate motivation to modify the Koch patent to arrive at the claimed invention. The *Deuel* case is instructive here. In *Deuel*, the examiner

rejected claims drawn toward specific compounds in light of teachings in references that suggested that there may be homologs between species. *See In re Deuel*, 51 F.3d 1552, 1556, 34 U.S.P.Q. 2d 1210, 1258 (Fed. Cir. 1995). The Board affirmed the Examiner's rejection reasoning that when "the sequence of a protein is placed into the public domain, the gene is also placed in the public domain because of the routine nature of cloning techniques." *Id.* at 1557. The Federal Circuit overruled the Board's affirmance of the Examiner's rejection concluding that, with respect to the claims drawn toward specific compounds, "any motivation that existed was a general one, to try to obtain a gene that was yet undefined and may have constituted many forms." *Id.* at 1558. The same is true here, as the general disclosure of an alkyl group having 1 to 6 carbon atoms with 1 to 6 halogen atoms does not suggest or teach a compound having ^{18}F atoms in R_2 substituents of the kind claimed for PET, nor does the general teachings provide or suggest methods of synthesizing such compounds that may be used in PET. The existence of a general incentive, as stated in the Final Rejection, does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. *See id.*

At best, the teaching might be considered a motivation to try. But it is well settled that being "obvious to try" is not the appropriate standard under 35 U.S.C. § 103, and does not render the claimed invention obvious. *See id.* at 1559; *see also In re O'Farrell*, 853 F.2d 894, 902, 7 U.S.P.Q. 2d 1673 (Fed. Cir. 1988).

The Examiner's suggestion that motivation to produce the claimed R_2 exists because "all compounds under the genus have similar methods of use," is incorrect. (Final Rejection at page 3). It is well established that such generalizations "should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other." *See In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985) (the court overruled the Board's affirmance

of the Examiner's rejection of the pending claims as being obvious over a reference disclosing the use of a sulfur atom instead of an oxygen atom and the proposition that sulfur and oxygen are isologs of one another.). That is particularly true here due to the unique characteristics between handling different isotopes of fluorine and the multiply halogenated alkyl chains. The Examiner was required to provide a specific showing of motivation to make the needed modifications. *See Deuel*, 51 F.3d at 1558 (citing *In re Lalu*, 747 F.2d 703, 705, 223, U.S.P.Q. 1257, 1258 (Fed. Cir. 1984)) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). The Examiner failed to do so. Significantly, none of the claimed choices is suggested by the evidence of record and the Examiner pointed to nothing to show otherwise. Given the need for such choices, and the absence of any evidence that a person of ordinary skill would have been sufficiently motivated to make them, Applicants submit that the rejection for alleged obviousness should be withdrawn. *In re Bell*, 991 F.2d 781, 26 U.S.P.Q. 2d 1529 (Fed. Cir. 1993) (DNA sequence held to non-obvious in view of reference suggesting multiple possibilities and failing to suggest why among those possibilities one would seek the claimed sequence).

D. The Examiner Improperly Predicated The Rejection On The Incorrect Conclusion That The Koch Patent And The Claimed Compounds Are Homologs.

The Examiner's obviousness rejection, and in particular his "motivation" assertions, is based on the incorrect position that the "instant claims are homologs of the compounds of Koch et al." and that "one homologue is not such an advance over adjacent member of series as requires invention because chemists knowing properties of one member of series would in general know what to expect in adjacent members." (*See* Final Rejection, at p. 4) (citing *In re Henze*, 85 U.S.P.Q. 261 (1950)).

The Koch patent's amide nitrogen substituent and the claimed R_2 are not homologs of each other. Homologs of a compound have the same substituent group and differ from successive homologs by the number of CH_2 groups in the molecule. The compounds of the present invention are not homologs because they differ in both the number and kind of fluorine atoms on the R_2 substituent. The Examiner's position is thus unsupported.

Thus, when considered the Koch Patent's disclosure in its entirety, as the Examiner is required to do, the Koch patent does not provide a suggestion or teaching to make the claimed compounds of the present invention having the general formula $CH_2CX_2CHX_2$ wherein X is halogen or hydrogen and at least one carbon atom of said alkyl group is bound with at least one ^{18}F atom.

IX. Conclusion

For the foregoing reasons, the rejection of claims 20-22 and 27-32 under 35 U.S.C. § 103(a) as being obvious is improper and should be reversed. Applicants respectfully request that this patent application be remanded to the Patent Office with an instruction to withdraw the rejection and reconsider and allow the appealed claims.

Date: July 3, 2003

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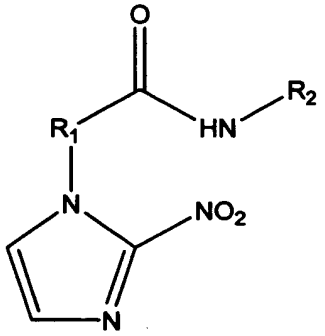
Assistant Commissioner for Patents
Washington, DC 20231

APPENDIX "A" TO APPELLANT'S BRIEF

20. A method for detecting tissue hypoxia in a mammal comprising: administering to the mammal a compound having the formula:



wherein R_1 is CH_2; and R_2 has the formula $CH_2CX_2CHX_2$, wherein X is halogen or hydrogen and at least 1 carbon atom of said alkyl group is bound with at least one ^{18}F; and imaging the portion of the mammal containing the tissue.

21. The method of claim 20 wherein the detection technique is PET.

22. The method of claim 20 wherein R_2 is $CH_2CH_2CH_2{}^{18}F$ and the detection technique is PET.

27. The method of claim 20 wherein the halogen is fluorine.

28. The method of claim 20 wherein R_2 is $CH_2CF_2CH_2{}^{18}F$.

29. The method of claim 20 wherein R_2 is $CH_2CF_2CH^{18}F_2$.

30. The method of claim 20 wherein R_2 is $CH_2CHFCH_2{}^{18}F$.

31. The method of claim 20 wherein R_2 is $CH_2CHFCH^{18}F_2$.

32. The method of claim 20 wherein R_2 is $CH_2CH_2CH^{18}F_2$.